DREB regulon: a key regulator of abiotic stress tolerance in plants

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DREB, the Dehydration Responsive Element (DRE)-binding proteins family is one of the largest families of transcription factors (TFs) that plays a significant role in the signaling network which modulates many plant processes. They belong to the AP2/ERF superfamily of transcription factors. The DREB TFs have been divided into two categories, DREB1 and DREB2. The common feature of all DREB genes is that they have three conservative regions, the EREBP/AP2 DNA binding domain, the N-terminal nuclear localization signal, and the Ser/Thr-rich region. This review summarizes recent studies highlighting the role of the DRE-binding family TFs in the tolerance to different abiotic stresses. The mechanisms by which DREB1 and DREB2 genes are expressed in response to stress have also been discussed.

Keywords: *Abiotic stress, transcription factors, DREB1, DREB2, over-expression, stress responses*

INTRODUCTION

During the last 50 years, it has been shown that abiotic stress factors influence plant growth and crop production significantly, and crop yields have evidently decreased or stagnated in economically important crops (Raza et al., 2019). Recently, climate changes have aggravated the negative effects of abiotic stresses on plant productivity. On the other hand, genetic advances in major crops for increased yields or for improved traits are restricted due to the complexity of plant mechanisms controlling important traits and the limited availability of germplasm for tolerance to certain stresses (Soares et al., 2019). Plants live in constantly changing environments, which can be unfavorable for their growth and development. The major environmental factors negatively affecting the geographical distribution of plants in nature are drought, salt, and temperature stresses. These factors decline agricultural and plant productivity and threaten food security. The recent climate changes exacerbate the adverse effects of these abiotic stresses (He et al., 2018). The study of stress signaling pathways and plant adaptation to adverse environments is of great importance. As plants sensitive to stress consume too much water and fertilizers, it is very important to improve stress resistance of plants for agricultural productivity and also for environmental sustainability.

Stress perception, signal transduction to cellular components, gene expression are molecular responses to abiotic stresses, which result in metabolic changes imparting stress tolerance (Singh et al., 2019). The genes induced by stress product metabolic proteins which protect cells from stress. They also regulate the downstream genes for signal transduction. According to the results of the large-scale transcriptome analysis, these gene products can be divided into two groups (Li et al., 2019; Cofen et al., 2019). The first group includes genes encoding proteins that protect the cells from the effects of water stress. These genes govern the accumulation of compatible solutes (key enzymes for osmolyte biosynthesis like proline, betaine, sugars, etc.); passive transport through membranes and energy-requiring water transport systems (water channel proteins and membrane transporters); and the protection and stabilization of cell structures from desiccation and damage by reactive oxygen species (the detoxification enzymes such as glutathione S-transferase, catalase, superoxide dismutase, ascorbate peroxidase, etc.); enzymes for fatty acid metabolism, proteinase inhibitors, ferritin, and

lipid-transfer proteins; and other proteins for the protection of macromolecules (LEA (*late embryogenesis abundant*) protein, osmotin, antifreeze proteins, chaperons, etc.). In transgenic plants, introduction or over-expression of genes encoding LEA proteins, proline synthetase or betaine synthetase, etc. has been suggested to provide tolerance to drought or high salinity. The second group comprises regulatory proteins that further regulate stress signal transduction and modulate gene expression and thereby the function in the stress response. They include various transcription factors (TFs) such as myelocytomatosis oncogene (MYC), myeloblastosis oncogene (MYB), basic leucine zipper (bZIP), NAM, ATAF, and CUC (NAC), dehydration responsive element binding (DREB), etc. suggesting the role of various transcriptional regulatory mechanisms in the stress signal transduction pathways; protein kinases (mitogen activated protein (MAP) kinase, calcium-dependent protein (CDP) kinase, receptor protein kinase, etc.); protein phosphatases and proteinases implicated in the regulation of signal transduction and gene expression (Baillo et al., 2019). Interacting with cis-elements in the promoter regions of various stress-related genes, the TFs up-regulate the expression of many downstream genes, thus impart stress tolerance (Agarwal and Jha, 2010).

The dehydration responsive elements

The DREB/CBF is an important class of transcription factors that binds to the drought responsive cis-acting elements (Konzen et al., 2019). This transcription factor class belongs to the ERF (ethylene responsive element binding factors) family of transcription factors. ERF proteins are a subfamily of the APETLA2 (AP2)/ethylene responsive element binding proteins (EREBP). EREBP are characteristic of plants. The EREBP (single AP2 domain) and AP2/family (two copies of AP2) are two subfamilies of the ERF family. The EREBP subfamily consists of two classes: ERFs and DREBs/CBFs. Binding to the GCC box found in the promoters of many pathogenesis-related (PR) genes, ERFs confer ethylene responsiveness. DREBs/CBFs bind to DRE/CRT which is the dehydration responsive element in the promoters of cold and dehydration responsive LEA genes including rd29A, rd17, cor6.6, cor15a, erd10 and kin1 (Dubouzet et al., 2003). In transgenic Arabidopsis plants, from the promoter of a stress inducible rd29A gene, a nine base pair conserved sequence (TACCGACAT), which is essential for rd29A induction under dehydration and cold stress, was identified (Chen et al., 2003). The DREB TFs also consist of two subclasses: DREB1/CBF and DREB2 (Lata and Prasad, 2011; Agarwal et al., 2017).

Role of DREB1 in abiotic stress-responsive gene expression

The Arabidopsis DREB1 subgroup includes six genes (Sakuma et al., 2002). Low temperature stresses strongly and transiently induce DREB1A/CBF3, DREB1B/CBF1, and DREB1C/CBF2 (Fowler and Thomashow, 2002). The activation of CBF1–CBF3 genes in response to low temperature was observed to be limited by the circadian clock. It suggests that their regulation has aspects in common with the regulation of Arabidopsis chlorophyll a/b-binding (CAB) genes (Fowler et al., 2005). OsDREB1A, OsDREB1B, OsDREB1C, and OsDREB1D have been isolated from rice (Dubouzet et al., 2003). A DREB1/CBF-type TF, ZmDREB1A was also found in maize (Qin et al., 2004). Based on the results of competitive DNA binding assays AtDREB1A protein could bind with the same efficiency to both ACCGAC and GCCGAC with the Role of DREB1/CBFs in cold-responsive gene expression; however, OsDREB1A protein preferentially binds to GCCGAC compared with ACCGAC. Although the Aloe DREB1 can bind to the DRE-cis element it may also bind to other cis-elements effectively. Therefore, it can function in a new cold-induced signal transduction pathway (Wang and He, 2007). Similar results were also obtained for OsDREBL which did not bind effectively to the CRT/DRE motif (Chen et al., 2003). Temporal gene expression studies performed on DREB/CBF genes in various crops showed the induction of these genes by abiotic stresses particularly low temperature, however, at different time periods. CBF1/DREB1B and CBF3/DREB1A transcripts were observed to accumulate after cold treatment, while CBF2/DREB1C transcripts accumulated slower. Their maximum accumulation

was detected after cold exposure and then a gradual decline occurred (Novillo et al., 2004). But in Arabidopsis, the CBF4 TF was rapidly induced by drought and ABA treatment but not by cold stress (Haake et al., 2002). OsDREB1A and OsDREB1B were induced soon after the exposure to cold, but did not respond to ABA treatment. OsDREB1A was induced by salt stress. But OsDREB1C was constitutively expressed during stress. OsDREB1D expression was not detected either under normal or stressful conditions. The accumulation of OsDREBL also occurred quickly within 30 min in response to low temperature, but not in response to ABA, NaCl, and dehydration (Chen et al., 2003). In wheat plants, the expression of the WCBF2 gene was found to be induced rapidly by low temperature and drought but not by ABA (Kume et al., 2005). PNDREB1 in Arachis hypogaea, was strongly upregulated by low temperature, and also responded to dehydration (Mei et al., 2009). However, Ca-DREBLP1 from hot pepper, which was rapidly induced by dehydration and high salinity, was not affected by cold stress (Hong and Kim, 2005). In Physcomitrella patens, the expression of PpDBF1 was also induced by drought, salt, cold and ABA treatments (Liu et al., 2007). The induction of DREB/CBF transcripts is organ-specific and proportional to the duration of the stress effect. AhDREB1 was highly expressed in roots and less in stems and leaves under salt stress. OsDREB1F was constitutively expressed in almost all the tissues and organs, including young leaves, young roots, mature leaves, mature roots, young panicles, and callus. Higher expression of OsDREB1F was observed in panicles and callus than in the other tissues (Wang et al., 2008). Salt, drought, and low-temperature cause a significant induction of the expression of the HvDREB1 gene in barley leaves (Xu et al., 2009). In leaves of soybean seedlings GmDREBa and GmDREBb were also induced by drought, cold and salt, whereas expression of GmDREBc was high in roots after drought, salt, and ABA treatments (Li et al., 2005).

Function of DREB2 in drought, salinity, and heat responsive gene expression

The DREB2 subfamily of the DRE-binding proteins is induced by drought and high-salinity stress, which indicates their important role in stress-responsive gene expression. The DREB2A and DREB2B were first isolated as cDNAs encoding DRE/CRT-binding protein from Arabidopsis (Liu et al., 1998). But among the eight DREB2-type proteins, DREB2A and DREB2B were considered as major transcription factors functioning under osmotic stresses (Sakuma et al., 2002). Despite the extensive investigations of DREB1 genes in many crops in response to different abiotic stresses, DREB2 expression has not been studied sufficiently. DREB2 homologous genes have been isolated from cereal crops also such as rice, wheat, barley, maize, pearl millet, and foxtail millet, which are economically important (Dubouzet et al., 2003; Xue and Loveridge, 2004; Egawa et al., 2006; Agarwal et al., 2007; Qin et al., 2007; Lata et al., 2011a). In barley, wheat, maize, and rice plants, DREB2 transcripts were found to be regulated by alternative splicing. Most of these transcripts showed transactivation abilities in yeast or plant cells (Egawa et al., 2006; Agarwal et al., 2007; Qin et al., 2007). In pearl millet, PgDREB2 was phosphorylated by total cell extracts and could not bind to DRE/CRT sequence (Agarwal et al., 2007). In Arabidopsis, DREB2A and its homologue DREB2B were found to be induced by dehydration and high salt stress, but not by cold stress and exogenous ABA. DREB2C expression was slightly induced by ABA, mannitol, and cold treatments. However, an enhanced level of DREB2C mRNA was detected after salt treatment (Lee et al., 2010). However, ABA and cold stress had a little effect on this transcript (Dubouzet et al., 2003). All five OsDREB2s from rice were thoroughly analyzed and it was found that the expression of OsDREB2A accumulated to the highest levels under the non-stress condition was increased slightly by high temperature, drought, and high salinity treatments, but not by low temperature (Matsukura et al., 2010). The OsDREB2B transcript level was found to increase significantly after 20 min of high temperature and 24 h of low temperature stress. Under control conditions, the transcript levels of OsDREB2C and OsDREB2E were found to be low and the abiotic stresses had no significant effects on them. Contrary to foxtail millet SiDREB2, wheat TaDREB1 and WDREB2, maize ZmDREB2A, and pearl millet PgDREB2 were responsive to cold stress (Dubouzet et al., 2003; Egawa et al., 2006;

Agarwal et al., 2007; Qin et al., 2007; Lata et al., 2011a). ZmDREB2A was also observed to respond to high temperature (Qin et al., 2007). In transgenic rice SbDREB2 in Sorghum was induced after drought, and then expression gradually decreased to primary levels (Bihani et al., 2011). Dehydration, salt, ABA, and auxin treatments caused an increase in the transcript level of chickpea CAP2 but the same effect was not observed with low temperature, salicylic acid, and jasmonic acid treatments (Shukla et al., 2006). The ABA treatment, cold, drought, and high salinity caused the induction of Populus euphratica PeDREB2 (Chen et al., 2009). In Salicornia brachiata, the expression of SbDREB2A transcript was induced by NaCl, drought, and heat stress (Gupta et al., 2010). Under normal growth conditions, AtDREB2A accumulation was observed in roots, stems, and leaves. In germinating seedlings DREB2C expression occurred in mature embryo and the cotyledons (Lee et al., 2010). According to Almoguera et al. (2009), sunflower HaDREB2 accumulated in all vegetative tissues. Under natural conditions, Chrysanthemum DvDREB2A was expressed in all organs. The highest transcript accumulation was observed in flowers while less accumulation occurred in roots, stems, and young leaves. SiDREB2 belonging to an A-2 type DREB family gene was found to be expressed in leaves, roots, and young and mature spikelets of foxtail millet, which suggests also its role in developmental pathways (Lata et al., 2011a).

Mechanisms of DREB gene regulation

DREBs are one of the important genes for crop improvement either through engineering stress tolerance or through crop breeding strategies since it is the major TF that binds to the cis-acting elements of most of the osmotic stress-inducible genes responsible for providing osmotolerance to the plants under stress conditions (Hussain et al., 2011). According to microarray analyses, most of these target stress-inducible genes contained the conserved DRE or DRE-related core motifs in their promoter regions (Maruyama et al., 2004). Both cDNA and Gene Chip microarrays have revealed more than 40 target genes of DREB1/CBF including TFs, phospholipase C, LEA proteins, KIN (cold-inducible) proteins, sugar transport proteins, desaturase, carbohydrate metabolism-related proteins, osmoprotectant biosynthesis proteins, and protease inhibitors known to function in stress response and are thought to be responsible for the observed stress tolerance of the transgenic plants (Fowler and Thomashow, 2002; Maruyama et al., 2004). As a result of the cDNA microarray analysis performed on transgenic Arabidopsis plants over-expressing AtDREB1A, it was revealed that 12 genes expressed 2-fold higher than in the wild-type, out of which six were stress-related genes namely, rd29A, kin1, cor6.6/kin2, cor15a, cor47/rd17, and erd10. However, the other six genes showed similarity to acclimatization protein, DC1.2, enolase, cysteine proteinase inhibitor, and erd4. Transgenic Arabidopsis over-expressing OsDREB1A showed 2-fold higher expression of six stress-related genes namely, cor15a, FLO5-21-F13, rd29A, rd17, AtGolS3, and FLO520-N18 (Dubouzet et al., 2003). According to these two studies products of these genes can function in stress tolerance in plants. It was also revealed that the over-expression of DREB genes driven either by the CaMV 35S or the rd29A promoter led to the accumulation of stress-inducible putative downstream genes such as LEA proteins and heat-shock-related genes, thus providing enhanced stress tolerance to plants (Sakuma et al., 2006a, b; Schramm et al., 2008). The accumulation and activation of these genes was suggested to adapt the plants to stress conditions. Furthermore, elevated contents of osmoprotectants such as free proline, and various soluble sugars like sucrose and raffinose, and metabolites like galactinol and myo-inositol were also detected in the over-expressor transgenic plants. It suggested that the enhanced stress tolerance of the transgenic lines was resulted from the prompt accumulation of these substances compared with wild type/control plants (Ito et al., 2006). Several previous studies revealed that overexpressing DREBs/CBFs enhances the expression of downstream target genes, especially those that encode for LEA proteins, including dehydrins and COR proteins. Therefore, a comparison of stress tolerance initiated by DREBs and those initiated by LEA proteins would be particularly interesting at this stage. As the mechanism of stress tolerance initiated by DREBs

has already been discussed in this section, the focus here is on the stress tolerance initiated by LEA protein genes. LEA genes are known to be associated with water or cold stress in plants and are active in tissues containing high ABA levels (e.g. seeds) (Tunnacliffe and Wise, 2007).

A reverse genetics approach (Novillo et al., 2004) revealed that CBF2/DREB1C acts as a negative regulator of CBF1/DREB1B and CBF3/DREB1A gene expression as cbf mutants were tolerant to drought, salinity, and freezing stresses. MYB15 which interacts with the promoter regions to repress their expression is another negative regulator of CBF/ DREB genes (Agarwal et al., 2006). The mechanisms of CBF/DREB1 gene expression in response to low temperature were studied also by Zhao et al. (2006), who provided a new perspective to the regulation mechanisms of the DRE mediated signaling pathway in cold-stress responses. Two groups of DREB-like genes namely, Group I and Group II were isolated. These groups were induced by low temperature, but Group I was expressed earlier than Group II. To activate the downstream genes in Brassica, the Group I DREBs could specifically bind to the DRE cis-acting element while Group II DREBs were transinactive and retained the ability to bind DRE sequence. Fluorescence quenching assays revealed the similarity between the DRE binding abilities of the two groups. The genes of both these groups worked in a competitive manner. Thus, Group II could suppress the trans-activation activity of Group I DREB in a concentration-dependent manner. The Group I DREBs express at the early stage of cold stress to switch-on the DRE-mediated signaling pathway, whereas the Group II DREBs express at the later stage of cold stress to switch-off this pathway. Thus, the low-temperature response through the CBF/DREB regulon is a tightly regulated mechanism to ward off any negative effects in plants. Actually, their uncontrolled expression in certain conditions may lead to dwarf phenotypes and reduced yields as well (Saibo et al., 2009). However, until now, the mechanism of activation of DREB2-type genes is not well-studied. It is suggested that for the activation of this class of proteins under stress conditions, not only transcriptional regulation but post-translational modification like phosphorylation may be necessary. It was also evident from the fact that the overexpression of AtDREB2A and OsDREB2A could not induce target stress-inducible genes (Liu et al., 1998; Dubouzet et al., 2003). As mentioned earlier a conserved serine/threonine rich region adjacent to the AP2/ERF domain may act as a putative site for phosphorylation. Under normal conditions, a negative regulatory domain has been identified in the AtDREB2A. Its deletion makes the protein constitutively active under stress conditions and also capable of up-regulating a number of drought, salt or heat-stress-responsive downstream genes (Sakuma et al., 2006a). According to the authors, the presence of a PEST sequence (RSDASEVTSTSSQSEVCTVETPGCV) in this negative regulatory domain that contained many phosphorylation target sites for protein kinases like PKC and CK2 (Salmeron et al., 2001). Contrary to Arabidopsis DREB2A protein, DREB2A of maize and pearl millet do not contain any PEST sequence (Agarwal et al., 2007; Qin et al., 2007). As a result of the in vitro ubiquitination assay, it was found that the DRIPs (DREB2A-interacting protein, C3HC4 RING domain containing proteins namely DRIP1 and DRIP2) mediate the degradation of DREB2A. The DRIP proteins were also found to function as E3 ubiquitin ligases and were capable of mediating DREB2A ubiquitination (Qin et al., 2008). Over-expression of full-length DREB2A protein was more stable in drip1 than in the wild-type background suggesting DRIP1 and DRIP2 as novel negative regulators in drought-responsive gene expression by targeting DREB2A to 26S proteome proteolysis (Nakashima and Yamaguchi-Shinozaki, 2010).

A putative MYC ICE1 (Inducer of CBF expression 1)-like TF probably plays an important role in activating CBF1/DREB1B, CBF2/ DREB1C and CBF3/DREB1A. Cold-induced phosphorylation is necessary for its activation and it can be regulated by HOS1 targeting the ICE1 protein for ubiquitination and subsequent degradation (Saibo et al., 2009). It was found that a SIZ1 (a SUMO E3 ligase)-dependent sumoylation can block ubiquitination of ICE1 (Miura et al., 2007), where sumoylation is a process that conjugates SUMO (small ubiquitin-related modifier) to a protein substrate. This alteration leads to activation/stabilization of the ICE1 protein and as a result, its activity controls

the expression of the CBF3/DREB1A gene (Saibo et al., 2009). As mutations in CAX1, a Ca 2+/H+ transporter, and CBL1, a Ca2+-sensor, affected the expression of DREB1/CBF genes, the DREB1/CBF genes were also regulated by Ca2+-related processes.

Enhanced tolerance to water and salt stress was detected in transgenic rice plants expressing barley HVA1, a Group 3 LEA gene. The transgenics were able to maintain relatively high levels of RWC and suffered less EL from cells. It is attributed to the ability of the HVA1 protein to protect cell membranes from damage during osmotic stress (Babu et al., 2004). Barley HVA1 was also able to confer better growth and higher WUE to transgenic wheat plants. Group I and II LEA protein genes from wheat were also found to confer protection against dehydration to transgenic rice (Cheng et al., 2002). DREB genes were also found to regulate the expression of specific LEA genes like COR14B in wheat (Morran et al., 2011). It is attributed to the fact DREBs/CBFs could regulate the activity of other downstream TFs, which may then regulate the specific expression of LEA genes. Therefore, a change in the expression level of a single DREB/CBF gene could regulate expression levels of other TFs leading to the activation of several downstream target genes, thus conferring stress tolerance to plants.

CONCLUSION

Plant responses to abiotic stresses are mostly overlapping and tolerance to one type of stress often confers tolerance to other stresses. Transgenic plants with DREB genes were found to be tolerant to multiple stresses. Thus, transgenic plants with drought or salt tolerance may also show tolerance to cold stress, resulting in enhanced volunteer potential in the next cropping season. A transgenic plant may confer to its wild relatives fitness advantage resulting in an increased weediness problem. The fitness advantage over surrounding plant communities may have unpredictable ecological consequences. Thus, it can displace local plant communities, and alter the plant interaction with non-target organisms. Emphasis should be placed on the problem formulation during environmental risk assessment for the evaluation of the increased weediness and invasiveness potential in abiotic stress tolerant transgenic plants engineered with DREBs. Unlike the previous reports of limited tolerance with single genes, engineering crop plants with DREB transcription factors has resulted in improved stress tolerance. Currently, further efforts are necessary to increase stress tolerance and improve the ability of plants to reduce productivity losses under abiotic stress conditions.

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DREB requlonu: bitkilərdə abiotik stresə davamlılığın əsas tənzimləyicisi

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DREB - dehidratasiyaya cavabdeh element (DRE)-birləşdirən zülallar bitkilərdə bir sıra prosesləri əlaqələndirən siqnal şəbəkəsində əhəmiyyətli rol oynayan transkripsiya faktorlarıdır. Bunlar AP2/ERF transkripsiya faktorları super ailəsinə daxildirlər. DREB transkripsiya faktorları DREB1 və DREB2 olmaqla iki kateqoriyaya bölünür. Bütün DREB genlərin ümumi xüsusiyyəti onlarda üç konservativ sahənin, EREBP/AP2 DNT birləşdirən domen, N-sonluqlu nüvə lokalizasiya siqnalı və Ser/Thr-zəngin sahənin olmasıdır. Bu icmal DRE-birləşdirən transkripsiya faktorları ailəsinin müxtəlif abiotik streslərə davamlılıqda rolunu işıqlandıran son tədqiqatları əhatə edir. DREB1 və DREB2 genlərin stresə cavab olaraq ekspressiya mexanizmləri də müzakirə olunmuşdur.

Açar sözlər: *Abiotik stres, transkripsiya faktorları, DREB1, DREB2, ifrat-ekspressiya, stresə qarşı cavab reaksiyası*